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Edited by Kiriakos Xenitidis and
Colin Campbell

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Short inter-pregnancy interval and schizophrenia: overestimating the risk

The short report by Gunawardana *et al*¹ succinctly argues that a short inter-pregnancy interval, a proxy for fetal undernutrition and stress, increases the offspring's risk of later schizophrenia. The authors hint at a causal relationship. This is compelling because it suggests that an affordable public health intervention via the promotion of dietary supplements in the postpartum period may later reduce schizophrenia prevalence.

Although the authors compare pre- and post-birth intervals and adjust for a number of confounders, their findings may still relate to bias and residual confounding. First, the timing of schizophrenia measurement may distort the prevalence and gender ratio of schizophrenia. This is important because a short inter-pregnancy interval is known to favour male offspring.² Looking at the cohort's median year of birth (1978) and the latest possible date of outcome measurement (2002), an individual's lifetime history of schizophrenia would be recorded at 24 years. As there is a significant gender variation in the age-specific incidence of schizophrenia,³ the median cohort age of 24 years is likely to bias the cohort towards male schizophrenia prevalence and overestimate the predictive validity of the short inter-pregnancy interval.

Second, the finding of no relationship between the post-birth inter-pregnancy interval and later schizophrenia does not discount residual confounders, including ethnicity and genetic factors, from contributing to the study's main findings. Genetic and familial factors, including ethnicity, are both associated with short inter-pregnancy intervals^{4,5} and schizophrenia.⁶ The current study did not mention adjusting for offspring ethnicity, although its design would make it possible. However, any epidemiological study would struggle to separate the prenatal effect of the inter-pregnancy interval from maternal–child genome sharing.

Epidemiological designs will only drive hypotheses so far in examining the causal relationship between prenatal micronutrient depletion and later psychopathology. That said, there would be scientific value in examining cohorts pre- and post-introduction of public health recommendations of periconceptional folic acid vitamin supplementation. In addition, further work analysing the correlates of prenatal nutrient depletion as additive risk factors could provide further evidence of a dose–response relationship. For example, are the risks of schizophrenia enhanced when there is a history of short pre-birth interval plus prior multiple births, concurrent breastfeeding or postnatal vitaminosis?

Introducing postnatal vitamin supplementation to reduce schizophrenia prevalence is an enticing idea; however, it would be important to use a variety of research designs to establish or exclude causality before implementing any change in public health policy.

- 1 Gunawardana L, Davey Smith G, Zammit S, Whitley E, Gunnell D, Lewis S, et al. Pre-conception inter-pregnancy interval and risk of schizophrenia. *Br J Psychiatry* 2011; **199**: 338–9.
- 2 Greenberg RA, White C. The sexes of consecutive sibs in human sibships. *Hum Biol* 1967; **39**: 374–404.
- 3 Thorup A, Waltoft BL, Pedersen CB, Mortensen PB, Nordentoft M. Young males have a higher risk of developing schizophrenia: a Danish register study. *Psychol Med* 2007; **37**: 479–84.
- 4 Rodgers JL, Kohler HP, Christensen K. Genetic variance in human fertility: biology, psychology, or both? In *The Biodemography of Human Reproduction and Fertility* (eds JL Rodgers, HP Kohler): 229–50. Springer, 2003.
- 5 Rawlings JS, Rawlings VB, Read JA. Prevalence of low birth weight and preterm delivery in relation to the interval between pregnancies among white and black women. *N Engl J Med* 1995; **332**: 69–74.
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Authors' reply: We agree with Downs & Jonas that it is important to establish whether the association between inter-pregnancy interval and schizophrenia is indeed causal, and that residual confounding is a potential explanation for our findings.

Residual confounding is, of course, a potential explanation for any association in observational epidemiological studies, as we discuss in our paper.¹ However, we believe that one of the strengths of our study is that we compare the relationship between the pre-birth inter-pregnancy interval and risk of schizophrenia with that of the post-birth inter-pregnancy interval and risk of this disorder. If the association between pre-birth inter-pregnancy interval and risk of schizophrenia is due to confounding, we would expect to observe a similar relationship for the post-birth interval, but we did not find this in our study. Although it is possible that there are confounders that are associated with pre-birth, but not post-birth inter-pregnancy intervals, this seems rather unlikely for most potential confounders.

For example, Downs & Jonas suggest that one such possible confounder is ethnicity, whereby individuals born to families from specific ethnic groups may be more likely to be conceived following a shorter pre-birth inter-pregnancy interval, as well as to have an increased risk of schizophrenia. However, if this were true then we would expect to see the same (confounded) relationship between post-birth inter-pregnancy interval and risk of schizophrenia. Comparing results for pre-birth and post-birth intervals allows us to be slightly more confident (although by no means certain) that unmeasured confounders do not provide an adequate explanation for our findings, and that the increased risk of schizophrenia following a shorter pre-birth inter-pregnancy interval might be causal. What it is about a shorter pre-birth inter-pregnancy interval that leads to an increased risk of schizophrenia is, as yet, unknown,¹ although arguments that this acts as a proxy for fetal undernutrition or exposure to stress have received the greatest support in the literature to date.^{2–5}

Downs & Jonas also argue that short inter-pregnancy intervals favour male offspring and that, given the gender variation in age-specific incidence of schizophrenia, this could lead to an

overestimation of the effect of a shorter inter-pregnancy interval. However, if male gender was indeed on the causal pathway between inter-pregnancy interval and schizophrenia, this would not, of itself, lead to a biased estimate of association between inter-pregnancy interval and schizophrenia. Furthermore, if male gender was indeed on the causal pathway, then adjusting for gender should lead to an attenuation of the association between inter-pregnancy interval and schizophrenia; however, adjusting for gender made no difference to our results,¹ indicating that gender is unlikely to be an adequate explanation as a mechanism for the association with shorter inter-pregnancy interval.

- 1 Gunawardana L, Davey Smith G, Zammit S, Whitley E, Gunnell D, Lewis S, et al. Pre-conception inter-pregnancy interval and risk of schizophrenia. *Br J Psychiatry* 2011; **199**: 338–9.
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- 5 Smits LJ, Essed GG. Short interpregnancy intervals and unfavourable pregnancy outcome: role of folate depletion. *Lancet* 2001; **358**: 2074–7.

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Care clusters and mental health Payment by Results

In their piece on mental health Payment by Results,¹ Macdonald & Elphick note ‘a lack of reassurance that costs per case within a cluster will be similar enough to support a viable tariff calculation’. This may underestimate the difficulties with the proposed new payment mechanism, which may have effects wider than disruption of nascent routine outcome measurement systems.

The UK has come relatively late to the process of payment reform for mental health services, but despite this it has followed an approach unlike that in other countries. The fundamental principle behind the care cluster approach seems to be the presumption that individuals with similar needs for care, as notionally defined by clusters of scores on the Health of the Nation Outcome Scales (HoNOS), will receive similar care and therefore incur similar costs. Importantly, costs themselves did not enter into the original process of defining care clusters.²

The approach pioneered by Fetter at Yale³ in developing the original Medicare prospective payment system in the 1980s was to combine consultation with clinicians and statistical analysis of clinical, administrative and cost data using variance reduction so that case-mix groupings are both expected to produce similar ‘clinical responses’ and also do in fact demonstrate acceptable homogeneity of costs. This approach was also followed by Australia and New Zealand,^{4,5} when they attempted to develop payment systems based on HoNOS. Achieving homogeneous costs within groups is crucial because it minimises the random risk to providers (the risk that appropriately incurred costs and therefore revenue differ randomly from those reimbursed). A typical cut-off for acceptable cost homogeneity is for each case-mix group to have a coefficient of variation of one or less (mean divided by standard deviation). It is also essential to make sure that factors relevant in resource use which may be more or less prevalent among different providers are also represented; otherwise there

may be an element of systematic risk, with certain providers being systematically underpaid and others systematically overpaid. Even when this more standard approach is followed, it may not be successful, especially in mental health, where cost variation is high. Infamously, the original Medicare prospective payment system was never implemented in specialist mental health units in the face of evidence that resource homogeneity was too low and that the system would systematically disadvantage those units, and has now been abandoned in favour of an across the board per diem payment system for psychiatric in-patients.⁶ Neither the Australian nor New Zealand systems were ever implemented.

In the light of the foregoing comments, it is perhaps not surprising that the Department of Health’s own pilot studies from 2006 demonstrate both that resource homogeneity of care clusters is unacceptably low, with only 1 of 13 clusters having a coefficient of variation of less than one, and also that far better homogeneity could have been achieved, especially for in-patients, had the standard variance-reduction approach been followed.⁷ At present, it seems to me that the lowest risk approach to reforming payment for mental health services is to adopt a basic system of activity-based funding, and use the data collected in this way, along with clinical and administrative data, as part of a slow and careful process of reform. Certainly, payment for mental health services in the UK is ripe for reform, as variations in resource use between providers are far wider than could be accounted for by any difference in case-mix.⁸ But this may not be the best way of approaching it.

- 1 Macdonald AJD, Elphick M. Combining routine outcomes measurement and ‘Payment by Results’: will it work and is it worth it? *Br J Psychiatry* 2011; **199**: 178–9.
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- 3 Fetter RB. *Health Care Financing Grants and Contracts Report: The New ICD-9-CM Diagnosis Related Groups Classification Scheme*. Health Care Financing Administration, 1983. Available from: <http://babel.hathitrust.org/cgi/pt?id=mdp.39015009571160>.
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- 7 Health and Social Care Information Centre Casemix Service. *Mental Health Casemix Classification Development: End Stage Report*. Health and Social Care Information Centre, 2006.
- 8 Audit Commission. *Maximising Resources in Adult Mental Health*. Audit Commission, 2010.

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The key to doing routine mental health outcomes well¹ is to make them relevant, meaningful and available to practitioners, service users and managers. The Health of the Nation Outcome Scales (HoNOS) is now a front-runner for a general outcome measure since it is required for Payment by Results, a new contracting system for mental healthcare in the UK. Only one HoNOS rating is currently required in order to allocate patients to Payment by Results care clusters, so managers have little incentive to take the extra step and mandate more than one HoNOS rating to assess the effectiveness of interventions. The simplest way to introduce outcome measurement with HoNOS would be to mandate at least two ratings, one at the outset of an intervention and one

at the close. A benchmark for this approach has been set by the Priory Group for HoNOS outcomes of in-patient stays (www.priorygroup.com/Personal-Site/About-Priory/About-Us/Healthcare-Outcomes/General-Psychiatry.aspx). Psychological therapists are ahead of the curve, since many already use a commercial outcomes tool (e.g. Clinical Outcomes in Routine Evaluation, CORE; www.coreims.co.uk) in their work to monitor treatment progress, to support reflection and to aid supervision. They also involve patients, who make their own ratings on a standard questionnaire. They have made outcomes relevant and meaningful. Could their experience help develop HoNOS as an outcome tool? The HoNOS could be put to work supporting practitioners. For example, HoNOS could inform referral and assessment systems, by helping select between primary and secondary care services. If no individual HoNOS item rating is greater than 2 (mild), then secondary services may not be indicated. Individual scale scores could also indicate priorities for interventions: a high score on 'hallucinations and delusions' and a low score on 'living conditions' could suggest a focus on treatment over accommodation (and *vice versa*). The HoNOS total and individual scale scores would also indicate progress and could be used in supervision. The HoNOS scores that fall below predetermined thresholds may indicate readiness for discharge. These could even be agreed as goals with patients. Co-producing HoNOS with service users and carers could balance the perspective of HoNOS as a clinician-rated measure. Getting all practitioners on board will need vision and effort. Gilbody *et al*² found that psychiatrists were not very interested in recording standardised outcomes. Feedback is crucial to engagement. Trusts should invest time to design their information systems so that they report person-centred outcomes directly to practitioners and teams in a meaningful format. Simply reporting outcome returns centrally would miss a huge opportunity to engage clinicians with outcomes, but still burden them with data collection. Outcomes information will create new challenges, for example the apparent ability to compare the effectiveness of teams and individual practitioners. For some, this could be intensely motivating or intimidating. The introduction of standard outcome measures should be done thoughtfully with ongoing input from service users, practitioners, managers and academics; or as Macdonald & Elphick put it: well.

Declaration of interest

Outcomes data affect my appraisal. I have a clinical information lead role in my trust.

- 1 Macdonald AJD, Elphick M. Combining routine outcomes measurement and 'Payment by Results': will it work and is it worth it? *Br J Psychiatry* 2011; **199**: 178–9.
- 2 Gilbody SM, House AO, Sheldon TA. Psychiatrists in the UK do not use outcomes measures. National survey. *Br J Psychiatry* 2002; **180**: 101–3.

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MacDonald & Elphick¹ have lucidly described the proposed introduction of Payment by Results into mental health. They mention, however, that 'concerns include the validity and reliability of the MHCT' (mental health clustering tool), and there is also the major issue of how cost can be firmly linked to the quality of services delivered.

The Department of Health approach to reliability has been to rely on local initiatives and to commission the development of an algorithm based on the MHCT to ensure that clusters are reliably allocated. Exactly why the Department of Health believes that this is possible by either route is not clear. Local initiatives are the

route to mayhem and none of the attempts at devising algorithms so far have been successful. The instrument on which the MHCT is based, Health of the Nation Outcome Scales (HoNOS), was not devised for this purpose. Additional items have been added but this was for clinical reasons. The HoNOS was devised as a clinical outcome measure, not for needs assessment and certainly not as a classification tool. Internationally recognised tools (e.g. Schedules for Clinical Assessment in Neuropsychiatry, Structured Clinical Interview for DSM Disorders) have been devised to classify conditions but these use a range of information (e.g. symptoms, beliefs and timescales), with specified criteria that have been and continue to be subject to international expert scrutiny.

A unit of costing must be directly related to quality and outcome measures or the UK will have the same problems as the USA have encountered in its payment systems. It is difficult to understand how clusters can be such units of cost unless there is a very substantial body of research investigating evidence for efficacy of interventions (e.g. cognitive therapy and medication) for individual clusters, and for the development and reliability testing of outcome measures – which would take years. Attempting to match cluster to pathway/intervention has to be done by using diagnosis as an intermediate step because that is where the evidence currently exists. The problem then is that each cluster relates to a number of guidelines and monitoring quality becomes complicated – as trusts, and previously the Department of Health, are finding in attempting to devise cluster pathways. General practice commissioners won't have the time, resource or inclination to undertake such complex monitoring – so cost will rule.

Broad diagnoses, as used by the National Institute for Health and Clinical Excellence, have proved satisfactory for clinical purposes and have readily available, reliable and applicable outcome measures² and, although diagnosis alone is not sufficient for costing, in combination with clinical pathways³ they can be costed and used for tariffs with a much better chance of reliability and homogeneity. The very limited data that have been produced so far are promising (available on request) but there needs to be more extensive examination of data. The Department of Health needs to take a lead because trusts are not going to re-analyse their data using diagnosis and allocation to pathways unless the Department of Health asks them to do so.

As MacDonald & Elphick¹ describe, outcome measurement is needed in any system and clustering has been very effective at promoting use of HoNOS. However, combining diagnosis and pathways could provide a simpler, practical approach to gathering data for costing and tracking change than can making use of clusters. It would also lead to an improved quality of care by linking cost directly to the use of evidence-based guidelines and care pathways by empowered patients, carers, providers and commissioners.

- 1 MacDonald AJD, Elphick M. Combining routine outcomes measurement and Payment by Results: will it work and is it worth it? *Br J Psychiatry* 2011; **199**: 178–9.
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- 3 NHS South Central. What services can I expect? NHS South Central, 2011 (http://www.sha.nhsdigital.org.uk/index.php?option=com_content&view=article&id=203&Itemid=31).

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Authors' reply: We are delighted that these responses to our editorial expand on issues that we could not explore more fully. Tulloch gives a cogent account of the typical methodology – not now being followed in England – for deriving case-mix groupings and finds the present plan wanting. He suggests a slow, careful change to commissioning based on activity and case-mix. Kingdon *et al* make the case for a system in which both diagnosis and care pathways are central in costing and thus purchasing, only *en passant* asking the crucial question of how (not whether) cost can be firmly linked to the quality of services delivered.

Both letters focus on which type of data should be chosen. The intended benefit of case-mix systems is to improve the direction of resources towards the greatest local need. If that were the only eventual use of the data items under discussion then mental health units should collect whichever (activity counts, clusters, diagnoses, pathways, etc.) best satisfy criteria such as Fetter's, as Tulloch implies. But data, once collected, have many other uses and misuses.

Kingdon *et al* argue on theoretical grounds that diagnostic categories should be better indicators than clusters of the type and quantity of care that is required by patients. Yet as Tulloch points out, findings from international analysis of variance studies of actual resource consumption within diagnostic groupings have tended to lead to their abandonment. We can add that similar methodology was used in mental health services in England from the early 1990s by the National Health Service Information Authority, testing both diagnostic and multidomain descriptors of patients' problems, in national and multi-site trial data-sets.¹ Diagnostically defined healthcare resource groups were abandoned by the Department of Health, not only because of the modest reduction in variance achieved, but also because of resistance by non-psychiatrists to the collection of diagnostic data. There was also resistance to informatics in general by a substantial proportion of clinicians, including senior Royal College of Psychiatrists' leaders at the time, although that is no longer the case.² Clusters were seen by policy makers as more likely to be acceptable. The fact that they become mandatory on 31 December 2011 with only this discussion in the *Journal* suggests that this approach is working.

As Kingdon *et al* point out, diagnostic categories enable us to use therapeutic research findings to decide which type of drug or psychosocial approach is chosen, but that does not much affect overall costs, and people often retain the same diagnosis throughout many life changes. By contrast, multidomain scores include more factors that indicate whether someone currently needs admission or frequent contact with paid professionals, which are the main financial determinants. And since the mental health clustering tool (MHCT) includes symptomatology ratings, and separates clusters into broad diagnostic groups anyway, the statistical benefits of diagnosis have not been entirely lost. Until there is more empirical evidence from costing studies, the relative merits of diagnostic versus multidomain data will remain debatable. Of course their value in outcomes and other quality monitoring, and predicting prognosis, must also be considered in developing mental health informatics generally. Prognosis is important because there is more 'value' in resolving a situation that would otherwise become chronic.

We do not support the automatic assignment of patients to any form of treatment, pathway or package of care on the basis of MHCT scores alone. The data may raise retrospective questions about clinical judgements, but should not replace them.

So what should we be doing about commissioning? Tulloch suggests in effect returning to the 1993 position and starting again. We do not think this is possible; while we looked away, boats were burnt. Kingdon *et al* propose the combination of diagnoses with

pathway data for costing purposes, but do not say quite how. The strong argument against using intervention counts, pathway data or other activity measures on their own for remuneration is that there is no safeguard against unnecessary, ineffective or inefficient interventions or pathways. Tariff 'matrices' in which prices are applied to cells containing both broad diagnoses and clinical management data have been proposed in the past,¹ but as we said above, they were abandoned. The large number of resulting categories should theoretically reduce costing variance, but it may be that commissioners would not in practice be able to use them effectively.

Yeomans concentrates on Routine Clinical Outcomes Measurement (RCOM), arguing strongly for its development and enhancement, while wisely refraining from almost suggesting 'Payment by Outcomes', which would violate Goodhart's law, succinctly put by Strathern: 'When a measure becomes a target, it ceases to be a good measure'.³ We agree with nearly all his points, especially on the importance of feedback, which are, notwithstanding the dated survey he quotes, already coming to pass in some parts of England, as are developments in Patient-Reported Outcomes Measures (PROMs). Efforts to usefully involve HoNOS in clinical work itself are being reported, although from the other end of the earth.⁴ As he says, HoNOS are a start but not the last word in outcomes measures, and we would caution against using them for thresholds for referral or discharge. Validity in groups is no guarantee of validity in individual cases.

With exceptions, we have been slow to grasp the twin nettles of outcomes and costing of services, and if we are to regain the initiative, we have to think widely and deeply about what systems we think will work best for service users, even while change in these very systems is accelerating. A start would be made when trusts have clinical, outcomes, intervention, costing, human resource and finance data on the same spreadsheets for themselves.

Declaration of interest

A.M. receives payment for training in HoNOS65+.

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Dissociation: a valid concept?

I was saddened by Harold Merskey's review of the second edition of *Attachment, Trauma and Multiplicity: Working with Dissociative Identity Disorder* (edited by Valerie Sinason).¹ My sadness was not primarily caused by his critical assessment of some of the material presented, but by his inference that dissociative identity disorder and dissociative disorders in general do not exist. Anyone unfamiliar with dissociative disorders reading his comments would be forgiven for being persuaded of this.

Dissociative disorders have been recognised in both DSM-IV and ICD-10 for some 25 years now. Yet among psychiatrists in particular, they continue to be denied or misdiagnosed, causing serious re-traumatisation for a significant number of patients.

Merskey writes of the absence of 'critical statement[s] by a professional society', but fails to cite the acknowledged leaders in the field, the International Society for the Study of Trauma and Dissociation (ISSTD; www.isstd-d.org) and the European Society for Trauma and Dissociation (ESTD; www.estd.org). The ISSTD includes among its members a number of eminent psychiatrists and psychologists and it has produced extensive online guidelines on treatment. The charity First Person Plural, in association with the ESTD and Cheshire & Wirral Partnership NHS Foundation Trust, has produced a training and information DVD.²

Furthermore, the National Institute for Health and Clinical Excellence's guidelines accept the existence of dissociative disorders. It has not yet produced a treatment protocol for this condition and recommends that clinicians follow the guidelines of the best informed organisation (www.isstd-d.org/education/treatmentguidelines-index.htm).

It should be noted that many psychiatric services and community mental health teams across the country are now implementing treatment protocols for dissociative identity disorder and dissociative disorders that are not only effecting significant changes for patients but are also bringing about cost savings for services.³

Declaration of interest

R.A. is President of the European Society for Trauma and Dissociation.

- 1 Merskey H. Book review: *Attachment, Trauma and Multiplicity: Working with Dissociative Identity Disorder*. *Br J Psychiatry* 2011; **199**: 347–8.
- 2 First Person Plural. *A Logical Way of Being: The Reality of Dissociative Identity Disorder and Other Complex Dissociative Conditions* (DVD). FPP (<http://www.firstpersonplural.org.uk>).
- 3 Lloyd M. How investing in therapeutic services provides a clinical cost saving in the long term. *Health Serv J* 2011; 1 Sept.

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Author's reply: Dissociation begins with hypnotists, was developed by Janet, promoted by Freud and ruined by the absurdities of multiple personality disorder.¹ Consider Janet² hypnotising 'Lucie', an alternative personality of this patient producing automatic writing:

Q. 'How are you?'
A. 'I don't know.'
Q. 'There must be someone there who hears me.'
A. 'Yes.'
Q. 'Who is it?'
A. 'Someone other than Lucie.'
Q. 'Ah, Indeed!'
A. 'Another person.'
Q. 'Would you like us to give her a name?'
A. 'No.'
Q. 'Yes it will be more convenient.'
A. 'Alright, Adrienne.'
Q. 'Very well Adrienne. Do you hear me?'
A. 'Yes.'

In 1889 Binet observed that Janet '... himself created her by suggestion'.³

Hacking⁴ showed that the first 19th-century fugue states in young men were in French military conscripts exploiting the novel

long-distance continental railways. In older persons fugues are only found with dementia. Experimental attempts by excellent social psychologists over 60 years have completely failed to replicate repression⁵ and dissociation. Freud's own accounts of his cases with alleged repression/dissociation were completely unreliable,⁶ particularly as shown in the Freud–Fliess correspondence.⁷ Further, Pope *et al*⁸ have shown that a phenomenon like dissociation (i.e. losing complete trace of some important event and then recovering it through memory) has not been found so far in world literature preceding 1786, and by then Mesmer was actively using hypnotic procedures. If dissociation is a genuine human experience, it is remarkable that it was not known before that time.

There is no case of proven 'dissociation' fulfilling Pope's criteria without organic disorder, although many cases of alleged dissociative memory loss exist, not to mention the generally rejected syndrome of dissociative identity disorder, of which dissociation is the artefactual foundation no matter how much the name or term may be changed.

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Childhood sexual abuse and chronic fatigue syndrome

We have read the important article on the premorbid risk markers for chronic fatigue syndrome in the 1958 British birth cohort¹ with a lot of interest. The authors reported that parental physical abuse, childhood gastrointestinal symptoms and parental reports of many colds were independently associated with self-reported chronic fatigue syndrome (CFS), after adjusting for psychopathology.

Notably, the authors did not comment on the fact that parental physical abuse, but not sexual abuse, was predictive of CFS, even though childhood sexual abuse is a well-documented risk factor for CFS. More precisely, chronic fatigue was significantly predicted by childhood sexual abuse in a population-based study by Taylor & Jason.² Also, childhood sexual abuse and emotional abuse were most effective in discriminating CFS cases from control individuals in two population-based studies by Heim *et al* (as well as emotional neglect in one of these studies).^{3,4} A possible reason for this inconsistency is the relatively low frequency of sexual abuse in the study by Clark *et al*¹ (6.3 %), compared with its frequency in the others studies (> 26%).^{2–4}

Interestingly, there may be a differential clinical effect according to the subtype of childhood trauma. In the study by Taylor & Jason,² a history of childhood sexual abuse emerged as a significant predictor of post-traumatic stress disorder. Furthermore, significant correlations between scores on a trauma questionnaire and scores for depression, anxiety and post-traumatic stress were observed by Heim *et al.*³ These correlations remained unchanged when the analysis was restricted to the subscales sexual abuse and emotional neglect.

Recently, our research group examined the impact of childhood trauma in a well-described tertiary sample of patients with CFS. In accordance with the previously mentioned population-based studies, childhood sexual harassment was the best predictor of psychological symptoms in CFS (unpublished data). Taken together, these data emphasise the importance of childhood sexual abuse as a premorbid risk marker for CFS.

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Clozapine v. chlorpromazine in treatment-naïve first-episode schizophrenia

Girgis *et al.*¹ present data on the usefulness of clozapine versus chlorpromazine in patients with first-episode schizophrenia. The authors must be complimented for conducting a follow-up study of the same cohort after 9 years and being able to have such a high retention rate. Further, the study provides information with respect to the naturalistic setting, reflecting the true clinical situation, and the authors have taken care of possible confounders with appropriate statistical analysis proper explanation. However, there are certain issues with the study. First, the title of the article is somewhat misleading because the randomisation phase of the study was only for the initial 2 years and after that the patients received treatment at the discretion of the clinicians. The title would have been appropriate if the authors were describing the outcome in terms of efficacy/effectiveness and side-effect profile by using survival analysis focusing on either of the medications. But actually the authors describe the effect of clozapine and chlorpromazine for the initial 1 year and outcome at the 9-year follow-up. Second, we need to understand that there are controversies in relation to the definition of first-episode psychosis and the definition used by the authors may appear to be very broad.² Third, the sample size in each treatment group that remained on the same medication (clozapine ($n=21$) or chlorpromazine ($n=8$)) at the 9-year follow-up is too small to

generalise. Hence, to conclude that there is no difference between clozapine and chlorpromazine with respect to effectiveness would be wrong. Fourth, the authors also conclude that there is no difference in metabolic and other side-effects between the two groups; besides having incomplete baseline data for weight there is no mention of other metabolic variables such as high-density lipoprotein, triglyceride and blood pressure. Fifth, more than half of the study sample (55% of the chlorpromazine group v. 73% of the clozapine group) was not on any anti-psychotic medication at 9-year follow-up, but the authors have not elaborated about their clinical status. Last of all, a quarter of participants (24%) were diagnosed with schizophreniform disorder which might have directly affected the outcome as this group of disorders is considered to have better outcome than schizophrenia.

- 1 Girgis RR, Phillips MR, Li X, Li K, Jiang H, Wu C, et al. Clozapine v. chlorpromazine in treatment-naïve, first-episode schizophrenia: 9-year outcomes of a randomised clinical trial. *Br J Psychiatry* 2011; **199**: 281–8.
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Authors' reply: We appreciate Nebhinani & Grover's interest in our study¹ as well as the opportunity to respond to the six comments. First, our study was analysed using the intent-to-treat principle. Implicit in the intent-to-treat principle is that the outcome is not the effect of treatment *per se*, but rather the effect of initial assignment irrespective of treatment(s) received.² Second, we agree that there are controversies as to the definition of first-episode psychosis.³ As reported by Breitborde *et al.*, 'duration of psychosis' possesses the most construct validity, followed by other criteria, such as 'duration of antipsychotic medication use' and 'first treatment contact'.³ We conservatively identified individuals with first-episode schizophrenia using both duration of psychosis and duration of antipsychotic medication use as two of our criteria. Furthermore, we included a maximum age criterion (i.e. 40 years old at the time when symptoms began) and symptom criteria to further narrow and restrict our study participants to those who are most likely to have first-episode psychosis. Third, our conclusions and main outcomes used the intent-to-treat principle and were based on the entire sample, rather than primarily based on the 29 individuals who remained on their originally assigned medication after 9 years. We described characteristics of this smaller group, without an intent to generalise, owing to the obvious lack of representativeness in this subgroup of patients. Furthermore, it is important to note that the generalisability of a clinical finding is determined by the representativeness of the sample observed, rather than the sample size observed.

Fourth, as described in the article, we did not have any missing baseline data for weight for those participants whose weights were included in our metabolic analyses. In addition, we disagree that we indicated that there were no differences in side-effects between the two groups. Rather, we descriptively reported differences in tardive dyskinesia and agranulocytosis between the two treatment groups. Finally, we did not claim that the metabolic findings in this study are generalisable, but we do agree with Nebhinani & Grover that it would have been valuable to report on additional metabolic indices (e.g. lipids and blood pressure). Unfortunately, these data were not available.

Fifth, we reported the average percentages of time that participants in each group took other antipsychotic medications or resumed the original medication during the follow-up period, rather than the percentages of individuals in each group on any treatment regimen at 9-year follow-up. Therefore, the results (55% for the chlorpromazine group and 73% for the clozapine group) represent averages over the entire 7-year period, rather than cross-sectional results at the 9-year follow-up time point. The clinical status of these patients over the entire 9 years of the study were reported in detail in the article, both in terms of symptom measures, functional status, global clinical status, medication status, side-effects, remission status and status in the study (i.e. still in the study or dropped out).

Finally, we agree that individuals with schizophreniform disorder are likely to have better outcomes than individuals with schizophrenia, by definition. However, all diagnoses were

randomly and equally assigned to the two treatment groups. Therefore, including this diagnosis is unlikely to have affected the between-group outcomes of this study.

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Corrections

Lay health worker led intervention for depressive and anxiety disorders in India: impact on clinical and disability outcomes over 12 months. *BJP*, **199**, 459–466. The following should be included in the Results paragraph of the summary, p. 459: Suicide attempts/plans showed a 36% reduction over 12 months (RR=0.64, 95%CI 0.42–0.98) among baseline ICD-10 cases. Strong effects were observed on days out of work and psychological morbidity, and modest effects on overall disability.

The online version of this paper has been corrected post-publication, in deviation from print and in accordance with this correction.

Clozapine and bladder control (letter). *BJP*, **199**, 518–519. The author of this letter is: Yatan Balhara, Department of Psychiatry, Lady Hardinge Medical College and Smt. SK Hospital, New Delhi, India 110001. Email: ypsbalhara@gmail.com.

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Short inter-pregnancy interval and schizophrenia: overestimating the risk

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